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SEVENTEENTH EDITION

THE MERCK MANUAL

OF

DIAGNOSIS AND THERAPY

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Published by MERCK RESEARCH LABORATORIES
Division of MERCK & CO., INC.
Whitehouse Station, N.J.
1999

THE MERCK MANUAL

CENTENNIAL EDITION

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Library of Congress Catalog Card Number 1-31760
ISBN 0911910-10-7
ISSN 0076-6526

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tion, otitis media, and acute exacerbations of chronic bronchitis.

Adverse reactions: The adverse reactions are the same as those listed above for sulfonamides. TMP causes identical adverse reactions to SMX but less commonly. When it does, nausea, vomiting, rash, and folate deficiency (resulting in macrocytic anemia) most likely occur. AIDS patients have a high incidence of adverse effects, especially rash and neutropenia.

Administration and dosage: The usual oral dosage in adults is 2 regular-strength tablets (each tablet contains 80 mg TMP and 400 mg SMX) or one double-strength tablet (160 mg TMP and 800 mg SMX) bid. The usual oral dosage in children is 8 mg/kg TMP and 40 mg/kg SMX daily in 2 divided doses. The IV dosage in adults and children is 12 mg/kg TMP and 40 to 60 mg/kg SMX daily in 4 divided doses. Single-dose therapy with 1 or 2 double-strength tablets has been used successfully for lower UTI in women.

Much higher dosages (20 mg/kg/day TMP and 100 mg/kg/day SMX in 4 divided doses) are used in the treatment of *P. carinii* pneumonia. Much lower dosages (40 mg TMP and 200 mg SMX each night) are used for prophylaxis of UTI. For prophylaxis of *P. carinii* pneumonia, 160 mg TMP and 800 mg SMX daily or 3 days/wk (for children, 5 mg/kg/day in 2 divided doses daily or 3 times/wk) is used.

Trimethoprim

For patients allergic to sulfonamides, TMP alone has been used mainly in the treatment of chronic bacterial prostatitis and in the prophylaxis and treatment of UTI. The pharmacology and adverse effects are listed under TMP-SMX, above. The dosage in adults for treatment of UTI is 100 mg po q 12 h or 200 mg once daily.

ANTIMICROBIAL CHEMOPROPHYLAXIS

The term antimicrobial chemoprophylaxis refers to the timely and judicious use of antimicrobial drugs to prevent infection, symptomatic disease caused by microorganisms. Although antimicrobial drugs play the pivotal role in chemoprophylaxis, immunologic defenses also contribute to the process.

Successful prophylaxis requires either target pathogens that are unlikely to develop resistance to the drugs used or clinical situations in which the duration of risk is measured in hours or days, thus permitting the effective use of antimicrobial drugs before resistance can emerge.

Prophylaxis Against Exogenous Pathogens

Prevention of infection by exogenous pathogens, organisms that are not usually part of the normal human flora, may involve destroying microbes before attachment to host cells, modifying the microbe to prevent attachment, or eradicating colonization before either tissue invasion or toxin production begins. Indications for prophylaxis include prevention of infections caused by *Streptococcus pyogenes* in patients with a history of rheumatic fever or rheumatic heart disease (see Ch. 270) and in those with recurrent cellulitis (see Ch. 112). Patients with animal and human bites are frequently treated. The choice of drug is controversial, but amoxicillin 500 mg/clavulanate 125 mg po tid for 5 days is often recommended for cat, dog, and human bites. Amoxicillin 500 mg qid or doxycycline 100 mg bid po is effective in preventing Lyme disease after tick bites; however, prophylaxis is seldom indicated because the risk of infection is generally low (see LYME DISEASE in Ch. 157).

Although *Neisseria meningitidis* and *Haemophilus influenzae* type b may occasionally colonize the upper respiratory tract of healthy persons, some persons exposed to patients with meningitis or other invasive diseases caused by these bacteria warrant prophylaxis. Household contacts, children with contact in day care centers, and others exposed to respiratory secretions of patients with invasive meningococcal disease (eg, physicians performing mouth-to-mouth resuscitation) should receive rifampin 600 mg po bid for 2 days if > 12 yr of age. Pediatric dosage is 5 mg/kg q 12 h po for 2 days if < 1 mo old and 10 mg/kg q 12 h po (maximum 600 mg) for 2 days if 1 mo to 12 yr old. Ceftriaxone 125 mg IM for children < 12 yr and ceftriaxone 250 mg IM for adults are other regimens. Alternatively, a single dose of ciprofloxacin 500 mg po can be given to adults older than 18 yr. If unvaccinated household contacts of patients with invasive disease caused by *H. influenzae* type b are children < 4 yr of age, all household members except pregnant women should receive oral therapy with rifampin 20 mg/kg (maximum 600 mg) daily for 4 days if > 1 mo old and 10 mg/kg for 4 days if < 1 mo old. This regimen should also be used with concurrent vaccine administration for susceptible children in day care centers, especially when two or more cases occur within 60 days and contacts include unvaccinated children < 2 yr old.

Persons traveling to endemic areas for malaria should receive prophylaxis (see Ch. 161). Although numerous studies have demonstrated that antimicrobial prophylaxis can reduce the frequency of travelers' diarrhea when traveling to high-risk areas for short durations, prophylaxis is controversial because of emerging resistance. Successful prophylaxis for this indication requires some knowledge of local susceptibility patterns for the target pathogens, usually toxin-producing strains of *Escherichia coli*. Most authorities prefer to reserve antimicrobial therapy for persons who develop diarrhea. For persons who must have prophylaxis, ciprofloxacin 500 mg/day po, norfloxacin 400 mg/day po, or two bismuth subsalicylate tablets po qid are effective. In some areas with low rates of antimicrobial resistance, oral trimethoprim-sulfamethoxazole (TMP-SMX) 160 mg/day (TMP) and 800 mg/day (SMX) or doxycycline 100 mg/day may be effective.

Antimicrobial prophylaxis is also used to prevent some viral infections. Prophylaxis with amantadine or rimantadine is effective during influenza A epidemics (see Ch. 162). Similarly, those sustaining parenteral exposures to blood or certain other body fluids from patients infected with HIV or those exposed to laboratory stocks of HIV may require prophylaxis with antiretroviral drugs (see Ch. 183).

Certain other uses of chemoprophylaxis are recommended, even though evidence from clinical trials is lacking. For the prevention of plague in exposed persons and laboratory workers, tetracycline 30 mg/kg/day po in 4 divided doses for 10 days or streptomycin 1 g IM daily for 1 wk appears to be effective. For prevention of pertussis in close contacts or colonized persons, erythromycin in an oral dose of 12.5 mg/kg qid (not to exceed 2 g/day) for 14 days is used. Chemoprophylaxis is widely used to prevent sexually transmitted diseases in the contacts of

active cases as well as in rape victims. Sexual partners of patients with gonorrhea, chancroid, lymphogranuloma venereum, nongonococcal urethritis, syphilis, trichomoniasis, scabies, pediculosis pubis, and infection caused by *Chlamydia trachomatis* receive standard therapeutic courses of the drugs normally used to treat these infections whether symptoms are present or not (see Ch. 164). Rape victims are treated with single doses of ceftriaxone 250 mg IM and metronidazole 2 g po and with doxycycline 100 mg po bid for 7 days. A single topical application of a 1% silver nitrate, 0.5% erythromycin ophthalmic ointment, or 1% solution of tetracycline ophthalmic ointment is used to prevent gonococcal and chlamydial infections in the eyes of newborns (see Ch. 260). Penicillin V, 20 mg/kg/day in 2 divided doses for children < 5 years and 250 mg po bid for children > 5 years, or amoxicillin, 125 mg po bid for children < 5 years and 250 mg po bid for children > 5 yr, is given to children with sickle cell disease or hypogammaglobulinemia or after splenectomy to prevent overwhelming pneumococcal infections. Although prophylaxis is controversial, some authorities recommend it until 5 yr of age or 5 yr after surgical removal of the spleen, whichever is longer. The 250-mg bid oral doses of penicillin V and amoxicillin have also been used in adults after splenectomy, but their efficacy is undetermined. To reduce infection rates in patients with chronic granulomatous disease, TMP-SMX in an oral dose of 8 mg/kg (TMP) and 40 mg/kg (SMX) bid for children and 80 mg/kg (TMP) and 400 mg/kg (SMX) for adults is widely used. Specific prophylactic guidelines exist for persons with AIDS and other causes of immunodeficiency.

Prophylaxis Against Endogenous Pathogens

Prevention of infection by endogenous pathogens, transient or permanent constituents of the normal human flora, usually involves prolonged treatment of chronically colonized persons to prevent spread of bacteria from the site of colonization to more vulnerable sites. For example, adult patients with recurrent skin infections caused by *S. aureus* have fewer infections while receiving orally administered clindamycin in a dose of 150 mg once daily. Hemodialysis pa... with nasal carriage of *S. aureus* and a h... of recurrent infections caused by this ... ism have reduced rates of infection ... orally administered rifampin in a dose ... mg bid for 5 days plus topical bacitr... nares for 7 days every 3 mo if nasal ... are positive for *S. aureus*. Mupirocin ... tranasally may substitute for bacitr... this regimen.

Children with recurrent otitis m... perience fewer recurrences when ... prophylactically. Likewise, wom... more than three UTIs per year have ... infection rates when treated proph... cally. Patients with compromised ... tracts and frequent recurrences of ... infection appear to have reduced ... infection when taking TMP-SMX ... floxacin 500 mg bid po.

In other cases, only a day or two ... microbial therapy is required to pr... fection. *Streptococcus agalactiae* ... in pregnant women and newborns ... reduced with intrapartum penicillin ... ampicillin therapy. Generally, only ... doses of antimicrobial drugs are ... mended to prevent endocarditis in ... with valvular or congenital heart ... when undergoing dental, surgical, ... procedures that are likely to induce ... remia (see Ch. 208).

Patients undergoing intensive chem... apy for malignant disease who have ab... neutrophil counts < 500 cells/μL (0.... are at high risk for bacterial infe... caused by resident flora of the GI tra... though controversial, prophylactic ... crobial therapy has been used to su... the endogenous flora of the bowel ... duce the rate of infection during the ... penic phase. Antimicrobial resistan... terns and trends in some medical ... argue against this approach to prophy... When used, prophylactic therapy for ... penic patients includes either oral n... (200,000-U lozenge qid or 500,000-U ... or tablet qid) or clotrimazole (10 mg t... 5 times/day) to combat *Candida* ... other yeasts plus oral antimicrobial ... Oral penicillin V 500 mg bid is take... either SMX/TMP 1600/320 mg bid or a ... roquinolone—ciprofloxacin 500 mg bi... floxacin 400 mg bid, or ofloxacin 400 m... Adding fluconazole to either regimen ... beneficial.

150 mg once daily. Hemodialysis p... with nasal carriage of *S. aureus* and a hi... of recurrent infections caused by this ... ism have reduced rates of infection ... orally administered rifampin in a dose o... mg bid for 5 days plus topical bacitra... nares for 7 days every 3 mo if nasal cu... are positive for *S. aureus*. Mupirocin bid ... tranasally may substitute for bacitra... this regimen.

Children with recurrent otitis me... perience fewer recurrences when t... prophylactically. Likewise, wome... more than three UTIs per year have re... infection rates when treated prophyla... cally. Patients with compromised ... tracts and frequent recurrences of ascend... infection appear to have reduced rate... infection when taking TMP-SMX or ... floxacin 500 mg bid po.

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Patients undergoing intensive chemothe... apy for malignant disease who have abso... neutrophil counts < 500 cells/μL for ≥1 ... are at high risk for bacterial infection ... caused by resident flora of the GI tract. Al... though controversial, prophylactic antim... crobial therapy has been used to suppre... the endogenous flora of the bowel and ... duce the rate of infection during the neutro... penic phase. Antimicrobial resistance pa... terns and trends in some medical cente... argue against this approach to prophylaxis. ... When used, prophylactic therapy for neutro... penic patients includes either oral nystati... (200,000-U lozenge qid or 500,000-U solution ... or tablet qid) or clotrimazole (10 mg troche ... 5 times/day) to combat *Candida* sp and ... other yeasts plus oral antimicrobial drug... Oral penicillin V 500 mg bid is taken with ... either SMX/TMP 1600/320 mg bid or a fluo... roquinolone—ciprofloxacin 500 mg bid, nor... floxacin 400 mg bid, or ofloxacin 400 mg bid. ... Adding fluconazole to either regimen is not ... beneficial.

In patients undergoing allogenic bone marrow transplantation, similar approaches are used to prevent infection during the prolonged phase of neutropenia before marrow engraftment.

Critically ill patients in ICUs who require intubation and mechanical ventilation for more than a few days are at high risk for developing bacterial pneumonia. Selective decontamination of the digestive tract, which is used extensively in Europe, combats this risk with topical and systemic antimicrobial therapy. It is designed to prevent oropharyngeal and GI colonization by aerobic gram-negative bacilli and *Candida* sp. In most studies, a paste containing polymyxin B, tobramycin or gentamicin, and amphotericin B or nystatin has been applied to the oral mucosa qid for the duration of intubation, and solutions of the same antimicrobial drugs have been administered orally or through a nasogastric tube several times a day. Cefotaxime 1 to 2 g IV q8h has also been administered for the first 5 days. Although such regimens have reduced infection rates in several studies, especially those for nosocomial pneumonia, there is no consensus recommending its use in the USA.

Prophylaxis in Surgery

Antimicrobial drugs are used perioperatively to prevent endogenous flora from gaining entry into normally sterile body sites. As a rule, prophylaxis is beneficial in so-called clean procedures only when prosthetic material or devices are being inserted and in clean-contaminated procedures, which are defined by transections of respiratory, GI, or GU tract mucosal surfaces. All of these surfaces are populated by the host's normal flora, which inevitably contaminate the wound and cause a high incidence of wound infections if prophylactic antimicrobial drugs are not administered.

Selection of antimicrobial drugs is based on the bacterial most likely to contaminate the wound during a specific procedure. Commonly recommended prophylaxes for various procedures are listed in TABLE 153–3. These recommendations may need to be modified in light of patient allergies, local resistance patterns, and local infection rates.

To effectively prevent surgical site infections, antimicrobial drugs are usually administered IV at the induction of anesthesia to ensure adequate concentrations in the wound when the first incision is made. De-

TABLE 153–3. ANTIMICROBIAL PROPHYLAXIS IN SURGERY

Category and Procedure	Adult Dosage*
Neurosurgical	
Craniotomy—high risk only, eg, re-explorations, microsurgery, and entry into sinuses or nasopharynx	Vancomycin 1 g IV and gentamicin 1.5 mg/kg IV preop; *or* cefazolin 1 g IV preop
CSF shunt placement—only in hospitals with high infection rates (15–20%)	Trimethoprim 160 mg IV and sulfamethoxazole 800 mg IV preop and q 12 h for 3 doses; *or* vancomycin 10 mg and gentamicin 3 mg injected into cerebral ventricle
Ophthalmic	
Extraction of lens, including insertion of prosthesis	Gentamicin, tobramycin, or neomycin-gramicidin-polymyxin B drops over 2–24 h; *and* cefazolin 100 mg subconjunctivally at end of procedure
Otolaryngologic	
Major head and neck surgery involving mucosa of oral cavity or pharynx	Cefazolin 1–2 g IV; *or* clindamycin 600–900 mg IV ± gentamicin 1.5 mg/kg IV preop and q 8 h for 2 doses
Cardiac	
Median sternotomy, coronary artery bypass grafting, valve surgery, and pacemaker insertion	Cefazolin 2 g *or* cefuroxime 1.5 g IV preop and q 4–6 h intraoperatively; *or* vancomycin 1 g preop

Table continues on the following page.

TABLE 153–3. ANTIMICROBIAL PROPHYLAXIS IN SURGERY (Continued)

Category and Procedure	Adult Dosage*
Noncardiac thoracic	
Pneumonectomy, lobectomy, and other resections or esophageal operation	Cefazolin 1–2 g IV preop and q 6 h for 24 [illegible]; vancomycin 1 g IV preop
Abdominal	
Gastroduodenal—with hemorrhage, malignancy, obstruction, and other high-risk features	Cefazolin 1–2 g IV preop *or* clindamycin [illegible] *and* gentamicin 120 mg IV preop
Gastric bypass	Cefazolin 1–2 g IV preop
Percutaneous gastrostomy	Cefazolin 1–2 g IV preop
Biliary tract (including ERCP)—with acute symptoms, previous surgery, jaundice, and other high risk features	Cefazolin 1–2 g IV preop; *or* gentamicin [illegible] preop and q 8 h for 3 doses
Appendectomy	Cefoxitin or cefotetan or cefmetazole 1–2 [illegible] preop and q 6 h for 3 doses if not perfo[illegible] *or* metronidazole 500 mg *and* gentami[illegible] mg/kg preop
Colorectal	Neomycin 1 g and erythromycin base 1 g [illegible] 2, and 11 PM on day before surgery if [illegible] parenteral agent(s) listed below; if em[illegible] cefoxitin or cefotetan or cefmetazole IV [illegible] and q 4 h for 3 doses; *or* metronidazole 6[illegible] IV and gentamicin 1.7 mg/kg IV preop [illegible] for 3 doses
Obstetric-gynecologic	
Cesarian section—high risk only, eg, premature rupture of membranes	Cefazolin 1 g IV after clamping cord and 6 [illegible] 12 h later
Abortion—2nd trimester instillation	Cefazolin 1 g IV preop and q 6 h for 2 doses
Abortion—1st trimester, with history of pelvic inflammatory disease, gonorrhea, or multiple partners	Penicillin G 1–2 million U IV preop and 3 h [illegible] *or* doxycycline 100 mg po before procedu[illegible] 200 mg 1/2 h afterward
Hysterectomy, vaginal or abdominal	Cefazolin 1 g IV preop and q 6 h for 2 doses; [illegible] doxycycline 200 mg IV preop
Orthopedic	
Arthroplasty, including replacements	Cefazolin 1–2 g IV preop and q 6 h for 3 dose[illegible] *or* vancomycin 1 g IV preop
Open reduction of fractures	Cefazolin 1 g IV preop and q 6 h for 3 doses
Lower limb amputation	Cefoxitin 2 g IV preop and q 6 h for 4 doses
Vascular	
Lower extremity or abdominal arterial surgery; lower extremity amputation for ischemia	Cefazolin 1–2 g IV preop and q 6 h for 24 h; [illegible] vancomycin 1 g IV preop and 12 h after pr[illegible] cedure
Urologic	
Prostatectomy—if bacteriuria is present	Cefazolin 1 g IV preop or other agent selected [illegible] basis of susceptibility tests
Penile prosthesis insertion	Cefazolin 1 g IV preop

*Agents, dosages, routes, and frequencies given are representative of current expert recommendations. Cefazolin remains highly favored because of its spectrum of bactericidal activity, long half-life, low cost, and low toxicity. Alternatives are primarily for patients with beta-lactam allergies.

preop = preoperation.

Adapted from Kernodle DS, Kaiser AB: "Postoperative infections and antimicrobial prophylaxis," in *Principles and Practice of Infectious Diseases*, ed. 4, edited by GL Mandell, JE Bennett, and R Dolin. New York, Churchill Livingstone, 1995, pp. 2742–2756 and from "Antimicrobial prophylaxis in surgery," *The Medical Letter* 39:97–102, 1997.

PHYLAXIS IN SURGERY (Continued)

Adult Dosage*
zolin 1–2 g IV preop and q 6 h for 24 h;
ncomycin 1 g IV preop
zolin 1–2 g IV preop *or* clindamycin 600
d gentamicin 120 mg IV preop
zolin 1–2 g IV preop
zolin 1–2 g IV preop
zolin 1–2 g IV preop; *or* gentamicin 80 m
op and q 8 h for 3 doses
ditin or cefotetan or cefmetazole 1–2 g IV
op and q 6 h for 3 doses if not perforated
netronidazole 500 mg *and* gentamicin 1.5
/kg preop
ycin 1 g and erythromycin base 1 g po
nd 11 PM on day before surgery if elective
enteral agent(s) listed below; if emergent
oxitin or cefotetan or cefmetazole IV
q 4 h for 5 doses; *or* metronidazole 500
nd gentamicin 1.7 mg/kg IV preop and
3 doses
lin 1 g IV after clamping cord and 6 h
later
lin 1 g IV preop and q 6 h for 2 doses
lin G 1–2 million U IV preop and 3 h
oxycycline 100 mg po before procedure
ng 1/2 h afterward
in 1 g IV preop and q 6 h for 2 doses; *or*
cycline 200 mg IV preop
in 1–2 g IV preop and q 6 h for 3 doses
ncomycin 1 g IV preop
in 1 g IV preop and q 6 h for 3 doses
in 2 g IV preop and q 6 h for 4 doses
n 1–2 g IV preop and q 6 h for 24 h; *or*
omycin 1 g IV preop and 12 h after pro
e
n 1 g IV preop or other agent selected on
of susceptibility tests
n 1 g IV preop

resentative of current expert recommendations
bactericidal activity, long half-life, low cost, and
-lactam allergies.

ections and antimicrobial prophylaxis," in Prin
GL Mandell, JE Bennett, and R Dolin. New York
robial prophylaxis in surgery," *The Medical Letter*

pending on the duration of the procedure and the pharmacokinetics of the drugs, additional doses may be required intraoperatively. The need for additional doses after the wound has been closed is highly controversial but is recommended by many authorities (see TABLE 153–3). The prophylaxis should not be continued > 24 h unless an active infection was discovered during surgery.

Prophylaxis Against Dormant or Latent Pathogens

Prevention of infection by dormant or latent pathogens, which are microorganisms already residing in the human host but not currently causing disease, requires either microbial eradication before immunologic defenses wane and allow the organisms to proliferate, or ongoing suppression of the remaining organisms, thereby precluding their multiplication and dissemination. For example, prophylaxis with acyclovir dramatically reduces the rate and severity of recurrences in persons with genital herpes who are subject to frequent attacks (see Ch. 164). Similarly, prophylactic therapy with isoniazid greatly reduces the likelihood of symptomatic disease in persons with latent TB infection (see Ch. 157).

Antimicrobial therapy is frequently used to prevent infections by latent or dormant pathogens in immunocompromised patients. Prophylaxis with TMP-SMX prevents *Pneumocystis carinii* pneumonia in persons undergoing intensive chemotherapy for various types of malignant disease or transplantation procedures. TMP-SMX, inhaled pentamidine, dapsone, and other drugs are used to prevent *P. carinii* pneumonia in patients with AIDS (see Ch. 163). Also, patients with AIDS, depending on their $CD4^+$ lymphocyte counts and exposures, often receive prophylaxis to prevent symptomatic disease caused by opportunistic infections (see Ch. 163). Similar targets for prophylaxis are encountered in transfusion and solid organ transplantation procedures (see Ch. 149).

154 / ANTIVIRAL DRUGS

The development of drugs against HIV has resulted in a dramatic expansion of new antiviral chemotherapeutic drugs. The applications of some of these drugs are being evaluated for other viral infections such as hepatitis B virus (HBV). Other advances include development of drugs with improved bioavailability for common infections such as herpes simplex virus (HSV) and varicella-zoster virus (VZV).

Chemotherapeutic intervention can occur before or at the time of viral particle attachment to host cell membranes, during uncoating of viral nucleic acids, by inhibiting a cellular receptor or factor required for viral replication, or by blocking specific virus-coded enzymes and proteins produced in the host cells that are essential for viral replication but not for normal host cell metabolism.

Idoxuridine

Idoxuridine (IDU) acts by irreversibly replacing thymidine in newly synthesized DNA and producing an abnormal and essentially nonfunctional DNA molecule. The drug acts on viral and host cell DNA and is *highly toxic to host cells*. Because of its high systemic toxicity, IDU has been limited to topical therapy of herpes simplex keratoconjunctivitis. Two topical ophthalmic preparations are available. One drop of a 0.1% solution is instilled conjunctivally q 1 h during waking hours and q 2 h at night. Treatment should be continued for 5 to 7 days after complete healing to lessen the chance of recurrence. IDU may cause irritation, pain, pruritus, and inflammation or edema of the eyelids; rare allergic reactions and photophobia have also been reported.

Vidarabine

Vidarabine (adenine arabinoside, ara-A) interferes with viral DNA synthesis and is effective in the treatment of HSV infections. Vidarabine appears less susceptible to the development of drug-resistant viral strains